UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/838,286	04/20/2001	Jacques Dumas	BAYER-14	9096

23599 7590 06/11/2007

MILLEN, WHITE, ZELANO & BRANIGAN, P.C.
2200 CLARENDON BLVD.
SUITE 1400
ARLINGTON, VA 22201

EXAMINER	
KWON, BRIAN YONG S	

ART UNIT	PAPER NUMBER
1614	

MAIL DATE	DELIVERY MODE
06/11/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 10/838,286
Filing Date: April 20, 2001
Appellant(s): Jacques Dumas

Jacques Dumas
For Appellant

EXAMINER'S ANSWER

This is in response to the Appellant's Appeal Brief filed February 01, 2007.

(1) Real Party in Interest

A statement identifying the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

The brief contains a statement concerning related appeals or interferences.

(3) Status of Claims

The statement of the status of the claims contained in the brief is correct

This appeal involves claims 50 and 52-56.

(4) Status of Amendments

No amendment after final has been filed.

(5) Summary of Claimed Subject Matter

The summary of claimed subject matter contained in the brief is correct.

(6) Grounds of Rejection to Be Reviewed on Appeal

The appellant's statement of the grounds of rejection to be reviewed on appeal in the brief is not correct.

The grounds for rejection to be reviewed are:

(1) the rejection of claims 50 and 52-56 under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for treating the specific disease mediated by p38 (e.g., rheumatoid arthritis, osteoarthritis and septic arthritis) by administration of the specific compounds of the Formula I (e.g., 4-ter-Butyl-2-pyridyl ureas), does not reasonably provide enablement for "a method of treating a disease mediated by p38 within a host" or "the treatment of a disease other than cancer" with the administration of "a compound of Formula I". This rejection is set forth in prior Office Action, mailed 06/28/2006.

(2) the provisional rejection of claims 50 and 52-56 under the judicially created doctrine of double patenting over claims 17-24, 26 and 30-32 of copending U.S. Application No. 09/776, 935 or claims 1, 3-4 and 7-11 of copending US. Application No. 10/086417. This rejection is set forth in prior Office Action, mailed 06/28/2006.

(7) Claims Appendix

The copy of the appealed claims contained in the Appendix to the brief is correct.

(8) Evidence Relied Upon

The following is a listing of the evidence (e.g., patents, publications, Official Notice, and admitted prior art) relied upon in the rejection of claims under appeal.

Chialda et al., Respiratory Research 2005, 6:36, pp. 1-19.

Kapoun et al. Molecular Pharmacology, abstract, 2006. www.mopharmaspetjournals.org.

Feldmann, M., Nature Immunology, 2001, Vol. 2, No. 9, pp. 771-773.

Cecil Textbook of Medicine 20th Edition, Vol. 1, Bennett et al., 1997.

Goodman & Gilman's The Pharmacological Basis of Therapeutics, 9th ed., 1996, pp. 51-58.

Dumas et al., Bioorganic & Medicinal Chemistry Letters, 10, 2000, pp.2047-2050.

Blink et al., The American Association of Immunologists, 2001, 166:582-587

(9) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

Claims 50 and 52-56 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for treating the specific disease mediated by p38 (e.g., rheumatoid arthritis, osteoarthritis and septic arthritis) by administration of the specific compounds of the Formula I (e.g., 4-ter-Butyl-2-pyridyl ureas), does not reasonably provide enablement for "a method of treating a disease mediated by p38 within a host" or "the treatment of a disease other than cancer" with the administration of "a compound of Formula I".

The claims 1-9 and 52-55 are drawn to a method for treating a disease mediated by p38 within a host, said method comprising to said host a compound of Formula I:

A - D - B (I)

or a pharmaceutically acceptable salt thereof, wherein

D is -NH-C(O)-NH-,

A is a

substituted t-butylpyridinyl, unsubstituted t-butylpyridinyl, substituted (trifluoromethyl)pyridyl, unsubstituted (trifluoromethyl)pyridyl, substituted isoquinolinyl, unsubstituted isoquinolinyl, substituted quinolinyl or unsubstituted quinolinyl, and

B is a substituted or unsubstituted, phenyl naphthyl, pyridinyl, pyrimidinyl, quinolinyl, isoquinolinyl or a bridged cyclic structure of the formula $-L(ML^1)_q$, wherein q is an integer of 1-3, and L^1 and L are each independently thiophene, substituted thiophene, phenyl, substituted phenyl, naphthyl, substituted naphthyl, pyridinyl, substituted pyridinyl, pyrimidinyl, substituted pyrimidinyl, quinolinyl substituted quinolinyl, isoquinolinyl or substituted isoquinolinyl and M is –O-, $-CH_2-$, -S-, -NH-, -C(O)-, $-O-CH_2-$ or $-CH_2-O-$, with cyclic structure L bound directly to D,

wherein the substituents for A are selected from the group consisting of halogen, up to per-halo, and Wn, where n is 0-3 and each W is independently selected from the group consisting of

C_{1-10} alkyl, C_{1-10} alkoxy, C_{3-10} cycloalkyl having at least a five cyclic members and 0-3 heteroatoms selected from N, S and O; C_{2-10} alkenyl, C_{1-10} alkenoyl, C_6-C_{14} aryl, C_7-C_{24} alkaryl, C_7-C_{24} aralkyl, C_3-C_{12} heteroaryl having at least 5 cyclic members and 1-3 heteroatoms selected from O, N and S, C_4-C_{24} alkheteroaryl having at least 5 cyclic members and 1-3 heteroatoms selected from O, N and S;

substituted C_{1-10} alkyl, substituted C_{1-10} alkoxy, substituted C_{3-10} cycloalkyl having at least 5 cyclic members and 0-3 heteroatoms selected from N, S and O; substituted C_{2-10} alkenyl, substituted C_{1-10} alkenoyl, substituted C_6-C_{14} aryl, substituted C_7-C_{24} alkaryl, substituted C_7-C_{24}

aralkyl, substituted C_3-C_{12} heteroaryl having at least 5 members and 1-3 heteroatoms selected from O, N and S, substituted C_4-C_{24} alkheteroaryl having at least 5 members and 1-3 heteroatoms selected from O, N and S,

-CN, $-CO_2R^7$, $-C(O)NR^7R^{7'}$, $-C(O)-R^7$, $-NO_2$, $-OR^7$, $-SR^7$, $-NR^7R^{7'}$, $-NR^7C(O)OR^{7'}$, $-NR^7C(O)R^{7'}$, with each R^7 and $R^{7'}$ independently selected from hydrogen, C_{1-10} alkyl, C_{1-10} alkoxy, C_{2-10} alkenyl, C_{1-10} alkenoyl, up to per halosubstituted C_{1-10} alkyl, up to per halosubstituted C_{1-10} alkoxy, up to per halosubstituted C_{2-10} alkenyl and up to per halosubstituted C_{1-10} alkenoyl, C_3-C_{10} cycloalkyl having at least 5 cyclic members and 0-3 heteroatoms selected from O, S and N, C_6-C_{14} aryl, C_3-C_{10} hetaryl having at least 6 cyclic members and 0-3 heteroatoms selected from O, S and N, up to per halo substituted C_3-C_{10} cycloalkyl having at least 5 cyclic members and 0-3 heteroatoms selected from O, S and N, up to per halo substituted C_6-C_{14} aryl and up to per halo substituted C_3-C_{10} hetaryl having at least 6 cyclic members and 0-3 heteroatoms selected from O, S and N,

where W is a substituted group, it is substituted by halogen, up to per halo, or by one or more substituents independently selected from the group consisting of –CN, $-CO_2R^7$, $-C(O)NR^7R^{7'}$, $-C(O)-R^7$, $-NO_2$, $-OR^7$, $-SR^7$, $-NR^7R^{7'}$, $-NR^7C(O)OR^{7'}$, and $-NR^7C(O)R^{7'}$, wherein R^7 and $R^{7'}$ are independently as defined above;

wherein the substituents for B are selected from the group consisting of halogen, up to per-halo, and J_n, where n is 0-3 and each J is independently selected from the group consisting of -CN, $-CO_2R^7$, $-C(O)NR^7R^{7'}$, $-C(O)-R^7$, $-NO_2$, $-OR^7$, $-SR^7$, $-NR^7R^{7'}$, $-NR^7C(O)OR^{7'}$, $-NR^7C(O)R^{7'}$, with each R^7 and $R^{7'}$ independently as defined for W above, C_{1-10} alkyl, C_{1-10} alkoxy, C_{3-10} cycloalkyl having at least five cyclic members and 0-3 heteroatoms, C_{2-10} alkenyl, C_{1-10} alkenoyl, C_{6-14} aryl, C_{3-12} hetaryl having at least a five cyclic members and 1-3 heteroatoms selected from N, S and O, C_{7-24} aralkyl, C_{7-24} alkaryl, C_4-C_{23} alkylheteroaryl having at least six members and 1-3 heteroatoms selected from O, N and S, substituted C_{1-10} alkyl, substituted C_{1-10} alkoxy, substituted C_{3-10} cycloalkyl having at least a five-members and 0-3 heteroatoms selected from N, S and O, substituted C_{2-10} alkenyl, substituted C_{1-10} alkenoyl, substituted C_6 - C_{14} aryl, substituted C_{3-12} hetaryl having at least five cyclic members and 1-3 heteroatoms selected from N, S and O, substituted C_{7-24} alkaryl, substituted C_7-C_{24} aralkyl and substituted C_4-C_{23} alkylheteroaryl having at least six members and 1-3 heteroatoms selected from O, N and S,

where J is a substituted group, it is substituted by halogen, up to per halo, or by one or more substituents independently selected from the group consisting of -CN, $-CO_2R^7$, $-COR^7$, $-C(O)NR^7R^{7'}$, $-OR^7$, $-SR^7$, $-NO_2$, $-NR^7R^{7'}$, $-NR^7C(O)R^{7'}$, and $-NR^7C(O)OR^{7'}$, with R^7 and $R^{7'}$ as defined above for W.

Further limitations include "A has 1-3 substituents selected from the group consisting of C1-10 alkyl, up to per halo substituted C1-10 alkyl, -CN, -OH, halogen, C1-10 alkoxy, up to per halo substituted Chow alkoxy and C3-10 heterocyclic moieties having at least 5 cyclic members and 1 to 2 heteroatoms selected from the group of consisting of nitrogen, oxygen and sulfur" (claim 52); "L1 is substituted 1 to 3 times by one or more substituents selected from the group consisting of-CN, halogen up to per halo, Cl-10 alkyl, C1-10 alkoxy,-OH, up to per halo substituted C1-10 alkyl, up to per halo substituted C1-10 alkoxy, -OR7, -SR7, -NR7R7' -CO2R7, -C(O)NR7R7', -C(O)R7 or-NO2, wherein each R7 and R7' is independently selected from hydrogen, Cl-10 alkyl, C1-10 alkoxy,C2-10 alkenyl, C1-10 alkenoyl, up to per halosubstituted C1-10 alkyl, up to per halosubstituted C1-10 alkoxy, up to per halosubstituted C2-10 alkenyl and up to per halosubstituted C1-10 alkenoyl" (claim 53); "a pharmaceutically acceptable salt of a compound of formula I is administered which is selected from the group consisting of a) basic salts of organic acids and inorganic acids selected from the group consisting of hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid, methanesulfonic acid, trifluorosulfonic acid, benzenesulfonic acid, p-toluene sulfonic acid (tosylate salt), 1-napthalene sulfonic acid, 2-napthalene sulfonic acid, acetic acid, trifluoroacetic acid, malic acid, tartaric acid, citric acid, lactic acid, oxalic acid, succinic acid, fumaric acid, maleic acid, benzoic acid, salicylic acid, phenylacetic acid, and mandelic acid; and b) acid salts of organic and inorganic bases containing cations selected from the group consisting of alkaline cations, alkaline earth

cations, the ammonium cation, aliphatic substituted ammonium cations and aromatic substituted ammonium cations" (claim 54); "the treatment of a disease other than cancer" (claim 55); "the condition within a host treated by administering a compound of formula I is rheumatoid arthritis, osteoarthritis, septic arthritis, tumor metastasis, periodontal disease, corneal ulceration, proteinuria, coronary thrombosis from atherosclerotic plaque, aneurysmal aortic, birth control, dystrophobic epidermolysis bullosa, degenerative cartilage loss following traumatic joint injury, osteopenias mediated by MMP activity, tempero mandibular joint disease or demyelating disease of the nervous system" (claim 56).

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 50 and 52-56 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for treating the specific disease mediated by p38 (i.e., rheumatoid arthritis, osteoarthritis and septic arthritis) by the specific compounds of the formula I (e.g., 4-ter-Butyl-2-pyridyl ureas), does not reasonably provide enablement for "a method of treating a disease mediated by p38 within a host", "the treatment of a disease other than cancer" with "a compound of Formula I ". The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

The factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. 112, first paragraph, have been described in In re Wands, 8 USPQ2d 1400 (Fed. Cir. 1988). Among these factors are: (1) the nature of the invention; (2) the state of the prior art; (3) the relative skill of those in the art; (4) the predictability or unpredictability of the art; (5) the breadth of the claims; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary. When the above factors are weighed, it is the examiner's position that one skilled in the art could not practice the invention without undue experimentation.

The claimed invention is directed to a method for the therapeutic treatment of all types of diseases mediated by p38 including cancer (claims 50, 52-54) or all types of diseases mediated by p38 other than cancer (claim 55), comprising administering said compounds represented by the Formula I.

The nature of the invention is extremely complex in that it encompasses anticipating multiple complex disorders having unrelated manifestations and subsequently administering the instantly claimed plethora of compound(s) represented by the formula.

The specification discloses that because inhibition of p38 leads to inhibition of cytokines (e.g., Tiff production, IL-1 and IL-8) and inhibition of proteolysis enzymes (e.g., MMP-1 and MMP-3) production, p38 inhibitors are useful in the treatment of the diseases or condition encompassed by the instant claims including arthritis, rheumatic fever, bone resumption, postmenopausal osteoporosis, sepsis, gram negative sepsis, septic shock, end toxic shock, toxic shock syndrome, systemic inflammatory response syndrome, inflammatory bowel diseases

including Cohn's disease and ulcerative colitis, Jarisch-Herxheimer reactions, asthma, adult respiratory distress syndrome, acute pulmonary fibrotic disease, Pulmonary sarcoidosis, allergic respiratory diseases, silicosis, coal worker's pneumoconiosis, alveolar injury, hepatic failure, liver disease during acute inflammation, severe alcoholic hepatitis, malaria including Plasmodium falciparum malaria and cerebral malaria, non-insulin-dependent diabetes mellitus DM), congestive heart failure, damage following heart disease, atherosclerosis, Alzheimer's disease, acute encephalitis, brain injury, multiple sclerosis including demyelation and oligodendrocyte loss in multiple sclerosis, advanced cancer, lymphoid malignancies, tumor metastasis, pancreatitis including systemic complications in acute pancreatitis, impaired wound healing infection, inflammation and cancer, periodontal diseases, corneal ulceration, proteinuria,myelodysplastic syndromes, systemic lupus erythematosus, biliary cirrhosis, bowel necrosis, psoriasis, radiation injury, toxicity following administration of monoclonal antibodies such as OKT3, host-versus-graft reactions including ischemia reperfusion injury and allograft rejections including kidney, liver, heart, and skin allograft rejections, lung allograft rejection including chronic lung allograft rejection (alliterative bronchitis)as well as complications due to total hip replacement, and infectious diseases including tuberculosis, Helicobacter pylori infection during peptic ulcer disease, Chaka's disease resulting from Trypanosome cruse infection, effects of Shiga-like toxin resulting from E. coli infection, effects of enter toxin A resulting from staphylococcus infection, meningococcal infection, and infections from Borealis burgdorferi, Treponema pallidium, cytomegalovirus, influenza virus, Theiler's encephalomyelitis virus, and the human immunodeficiency virus (H1V). See page 4, lines 30-31; page 5, lines 18-31; page 6, lines 14-26; page 6, line 27 through page 7, line 23.

With respect to the scope of enablement for the treatment of disease mediated by p38,

There are no known compounds of similar structure which have been demonstrated to treat (i) all types of diseases that are mediated thru p38 or (ii) all types of diseases other than cancer that are mediated thru p38. Since this assertion is contrary to what is known in medicine, proof must be provided that this revolutionary assertion has merits. The existence of such a "silver bullet" is contrary to our present understanding of pharmacotherapeutics.

Contrary to the instant invention, the art recognizes that the inhibition of p38 is not useful for the treatment of asthma (Chialda et al., Respiratory Research 2005, 6:36, pp. 1-19) and interstitial lung diseases and pulmonary fibrosis (Kapoun et al., Molecular Pharmacology, abstract, 2006, www.molpharmaspetjournals.org).

Furthermore, the art recognizes that drugs blocking p38 have been hindered by drug toxicity in human (Feldmann, M., Nature Immunology, 2001, Vol. 2, No. 9, pp. 771-773).

In addition, in cancer therapy art, it is recognized that different types of cancers affect different organs and have different method of growth and harm the body. Cecil Textbook of Medicine states that "each specific type has unique biologic and clinical features that must be appreciated for proper diagnosis, treatment and study" (see the enclosed article, page 1004). Also see In re Buting, 163 USPQ 689 (CCPA 1969), wherein 'evidence involving a single compound and two types of cancer, was held insufficient to establish the utility of the claims directed to disparate types of cancers'. Thus, it is beyond the skill of oncologists today to get an agent to be effective against all cancers or cancers mediated by p38.

The relative skill of those in the art of pharmaceuticals and the unpredictability of the art is high. Thus, based on the state of art knowledge, one having ordinary skill in the art would not have expected that the administration of said compounds would be able to treat all of disease condition mediated by p38. Pharmacological activity in general is a very unpredictable area. Note that in cases involving physiological activity such as the instant case, "the scope of enablement obviously varies inversely with the degree of unpredictability of the factors involved". See In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970).

Moreover, one of skill in the art would recognize that it is highly unpredictable in regard to therapeutic effects, side effects, and especially serious toxicity when and/or after administering to a host (e.g., a human) any compound represented by formula I. See "Goodman & Gilman's The Pharmacological Basis of Therapeutics" regarding possible drug-drug interactions (9th ed., 1996), page 51, in particular. Goodman & Gilman teaches that "The frequency of significant beneficial or adverse drug interactions is unknown" (see the bottom of the left column of page 51) and that "Recognition of beneficial effects and recognition of and prevention of adverse drug interaction require a thorough knowledge of the intended and possible effects of drugs that are prescribed" and the "The most important adverse drug-drug interactions occur with drugs that have serious toxicity and a low therapeutic index, such that relatively small changes in drug level can have significant adverse consequences" (see the right of page 51). In the instant case, in the absence of fully recognizing the identify of the member genus herein, one of skill in the art would not be able to fully predict possible adverse drug-drug interactions occurring with many combinations of any compounds having the claimed functional properties in the pharmaceutical compositions herein. Thus, the teachings of Goodman & Gilman

(in light of above mentioned Feldmann, M., Nature Immunology, 2001, Vol. 2, No. 9, pp. 771-773) clearly support that the instant claimed invention is highly unpredictable.

As mentioned above, the scope of the instant claims encompasses over 100 different types of diseases that may be related to p38 pathway mechanism. The specification discloses that inhibition of p38 inhibits both cytokine production (eg., TNFα, IL-1, Il-6, IL-8) and proteolytic enzyme production (e.g., MMP-1, MMP-3). See page 2, lines 10-13. The specification correlates to various diseases that are related to excessive levels of TNFα, excess or undesired matrix-destroying metalloprotease (MMP) activity or an imbalance in the ratio of the MMPs to the tissue inhibitors of metalloproteinases. See page 2, line 14 thru page 5, line 17.

The specification discloses the p38 inhibitory activity of the compounds in vitro assay (bottom of page 74 thru page 75) and the activity of the claimed inhibitors of p38 in murine lipopolysaccharide (LPS) model (in vivo) of TNFα production (page 75). However, the guidance given by the specification as to what types of ureas would be useful in a method of the instant invention is limited.

As stated above, the specification does not provide any competent evidence or disclosed tests that are highly predictive for the pharmaceutical use of the instant compounds for the treatment of all of the claimed disease conditions that are mediated by p38. As a result, one of skill in the art would be forced to perform an exhaustive search for the embodiments of any drugs having the function recited in the instant claim suitable to practice the claimed invention. Furthermore, one of skill in the art would have to determine not only which compounds inhibit p38, but which compounds actually treat all of diseases mediated by p38 mechanism without undue amount of experimentation.

Since the efficacy of the claimed compounds in treating all of complex diseases condition may have unrelated manifestation mentioned above cannot be predicted from a priori but must be determined from the case to case by painstaking experimental study and when the above factors are weighed together, one of ordinary skill in the art would be burdened with undue "painstaking experimentation study" to use the invention commensurate in scope with the claims.

With respect to the scope of enablement for "compound for Formula I",

There are no known compounds of similar structure which have been demonstrated to treat (i) all types of diseases that are mediated thru p38 or (ii) all types of diseases other than cancer that are mediated thru p38. Since this assertion is contrary to what is known in medicine, proof must be provided that this revolutionary assertion has merits. The existence of such a "silver bullet" is contrary to our present understanding of pharmacotherapeutics.

Contrary to the instant invention, it is known that the modification of urea core group with different substituents would have different physiological activity. For example, deletion of the two chlorine atoms or replacement of the chlorine atoms by methyl group in substituted phenyl ring attached to urea results in inactive compounds or weaker compound (Dumas et al., Bioorganic & Medicinal Chemistry Letters, 10, 2000, 2047-2050).

Furthermore, the art recognizes that drugs blocking p38 have been hindered by drug toxicity in human (Feldmann, M., Nature Immunology, 2001, Vol. 2, No. 9, pp. 771-773).

The relative skill of those in the art of pharmaceuticals and the unpredictability of the pharmaceutical art is very high. Note that in cases involving physiological activity such as the

instant case, "the scope of enablement obviously varies inversely with the degree of unpredictability of the factors involved". See In re fischer, 427 F.2d 833, 839, 166 USPQ 10, 24(CCPA 1970). Thus, one having ordinary skill in the art would not have predicted that all of the compounds represented by the instant formula would provide the claimed therapeutic utility without undue amount of experimentation.

The breadth of the claims encompasses plethora of compound(s) represented by the formula (over thousands compounds).

The instant specification discloses the preparation or synthesis of the instant compounds represented by the Formula I by known chemical reactions and procedures (page 18, line 3 thru page 22, line 2; page 29, line 3 thru page 74, line 3). Furthermore, the specification discloses the p38 inhibitory activity of the compounds in vitro assay (bottom of page 74 thru page 75) and the activity of the claimed inhibitors of p38 in murine lipopolysaccharide (LPS) model (in vivo) of TNFα production (page 75).

Although the specification provide sufficient guidance in how to make compounds that are suitable for the claimed invention, the specification fails to provide sufficient clarity in how to use it. The specification provides no guidance, in the way of enablement for the full scope of all compounds that are potentially suitable for the invention work similarly without known toxicity concern. The skill artisan would have not known that which compounds of the claimed compounds are capable of accomplishing the desired result of the claimed invention **without undue amount of experimentation**.

As discussed above, none of the specification provides enabling disclosure for the full scope of all compounds that would behave similar without known toxicity concern. There is no

demonstrated correlation that the tests and results apply to the claimed utility embraced by the instant claims.

Since the efficacy of the claimed compounds in treating all of complex diseases condition by all of compounds encompassed by the instant invention cannot be predicted from a priori but must be determined from the case to case by painstaking experimental study and when the above factors are weighed together, one of ordinary skill in the art would be burdened with undue "painstaking experimentation study" to use the invention commensurate in scope with the claims.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 50 and 52-56 are rejected under the judicially created doctrine of double patenting over claims 17-24, 26 and 30-32 of copending U.S. Application No. 09/776,935

Although the conflicting claims are not identical, they are not patentably distinct from each other because the scope of the copending application overlaps with the instantly claimed invention.

Both the instant application and the copending applications are directed to the administration of same compounds encompassed by the formula I to potentially same subject matter, for example patient having rheumatoid arthritis or osteoarthritis to treat same conditions. Although the instant invention differs from the copending application by the selection of the specific species from the generic formula, the copending application makes obvious the claimed invention since the species of the genus or subgenus are taught as having similar properties of the claimed invention.

Claims 50 and 52-56 are rejected under the judicially created doctrine of double patenting over claims 1, 3-4 and 7-11 of copending U.S. Application No. 10/086417.

Although the conflicting claims are not identical, they are not patentably distinct from each other because the scope of the copending application overlaps with the instantly claimed invention.

Both the instant application and the copending applications are directed to the administration of same compounds encompassed by the formula I to potentially same subject matter, for example patient having rheumatoid arthritis or osteoarthritis to treat same conditions. Although the instant invention differs from the copending application by the selection of the specific species from the generic formula, the copending application makes obvious the claimed

invention since the species of the genus or subgenus are taught as having similar properties of the claimed invention.

(10) Response to Argument

Appellant's arguments and remarks have been carefully considered, but are not deemed to be persuasive.

Appellant in his argument takes the position that the specification does reasonably provide enablement for treating diseases "mediated by p38" using the compounds of formula I and does enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with theses claims. Appellant asserts that the rejection is improperly based on bare allegations and conclusions, and that there is no evidence has been presented which would demonstrate that the guidance provided by the specification is inadequate to enable the use of the claimed compounds without undue experimentation. In appellants' Response filed February 02, 2007 (page 3, para. 2 to bridging page 4, para. 1 and page 5, para. 4 to bridging page 6, para. 1), appellant stated:

> **The specification cites a number of publications on pages 2-5, which are representative of the state of the art at the time of the invention. These publications have correlated TNF production and MMP production with a number of diseases. Since inhibition of p38 leads to the inhibition of TNF and MMP production, the p38 inhibitors of this invention will be useful in treating these diseases. No evidence has been presented to refute the findings or conclusions made in these publications or the present application. No evidence has been presented that any compounds of this invention, as inhibitors of p38, would not be effective in treating the diseases defined by this functional language. Furthermore, no evidence has been presented of the "undue experimentation " allegedly necessary to practice the invention commensurate in scope with the claims.**

> Only unsupported allegations and conclusions regarding the state of the art are provided to support the rejection such as, "There are no known compounds of similar structure which have been demonstrated to treat (i) all types of diseases that are mediated through p38 or (ii) all types of diseases other than cancer that are mediated by p38." Appellants wish to draw attention to US Patent No. 5,932,576, which contains claims to treating p38 mediated diseases using other small molecule compounds. The inventors of the '576 patent disclose the ability of the named compounds to inhibit p38 through in-vitro and in-vivo assays, as do the Appellants in their application. Others have defined the treatment of numerous inflammatory diseases using functional language similar to that used here. For example, US Pat. Nos.5,593,991 and 5,593,992 claim the treatment of "cytokine mediated diseases," with small molecules, the activity of which is demonstrated by in-vitro assays. Therefore, contrary to the Examiner's allegation, those skilled in the art have recognized and claimed that certain compounds can be effective for treating all types of diseases mediated by p38.

> In any event, the specification provides ample guidance as to how to prepare pharmaceutical compositions with the compounds of this invention and how to administer these compositions in the treatment of the diseases identified (see pages 22-26). The specification also provides dosage ranges for the various methods of administration (see pages 26-27). In fact, the specification provides more than it needs to, e.g., *in vitro* p38 kinase assays (and IC_{50} data) and *in vivo* assays. In similar fashion, one of ordinary skill in the art, by performing the same or similar tests, can, by routine experimentation, determine the activity levels of each of the claimed compounds in treating various diseases. This is absolutely routine in the field. Thus, appellants have provided more than adequate guidance (and examples) to enable the claimed invention. Given the extent of the disclosure provided, it would at most involve routine experimentation if any at all, for one of ordinary skill in the art to treat any one of the recited diseases with a compound of this invention.

Appellant's argument is not found persuasive. Contrary to the appellant's allegation, the examiner have cited various documents to support the examiner's position in determining why the instant invention does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these

claims. Particularly, the cited post-dated documents by the examiner, for example Chialda et al., Respiratory Research 2005, 6:36, pp.1-19 and Kapoun et al., Molecular Pharmacology, abstract, 2006, www. molpharmaspetjournals.org, teaches that the inhibition of p38 is not enabling for the treatment of asthma and pulmonary fibrosis which fall within the scope of broadly claimed "disease mediated by p38" (see page 7, lines 1-2 of the specification). Chialda et al. discloses that inhibition of p38 seems to be an unlikely target for anti-inflammatory therapy for asthma whereas Kapoun et al. discloses p38 activation is not involved in pathogenesis of pulmonary fibrosis. See abstract, "Results" and "Conclusion".

Furthermore, the examiner had provided with supporting evidences, for example Feldmann, M., Nature Immunolgy, 2001, Vol. 2, No. 9, pp. 771-773, Goodman & Gilman's The Pharmacological Basis of Therapeutics, 9th ed., 1996, pp.51, Cecil Textbook of Medicine, 20th Edition, Vol. 1, 1997 and Dumas et al., Biorganic & Medicinal Chemistry Letters, 10, 2000, pp. 2047-2050, to show (i) the unpredictability in art in designing drug that blocks p38 due to significant drug toxicity in human (page 772, column 3, lines 8-11 of the Feldmenan) or possible drug-drug interactions occurring with many combinations of any compounds having the claimed functional properties in the pharmaceutical composition (page 51 of the Goodman & Gilman), (ii) the general recognition in the art that sites of cancers are different for each type, as are diagnosis and treatment (page 1004 of the Cecil Textbook of Medicine) and (iii) the modification of urea core group with different substitutents would have different physiological activity, respectively.

As evidenced by the cited references by the examiner (see also van den Blink et al., The American Association of Immunologists, 2001, 166:582-587 for your reference), the requisite

nexus between p38 inhibition and in vivo assessment of usefulness of p38 inhibition as anti-cytokine and anti-proteolytic enzyme in patients with the broadly defined "a disease mediated by p38" including asthma, pulmonary fibrosis and infectious disease (e.g., pneumonia and tuberculosis), other than rheumatoid arthritis, osteoarthritis and septic arthritis, was not known at the time of the invention was made. As a result, one of skill in the art would have to undergo an undue amount of experimentation to use the invention commensurate in scope with the claims.

Examiner respectfully points out that in the determination of enablement one must take into account the guidance of the specification and the working examples (if any) presented in the specification. Appellant have not specifically described the compounds tested in the p38 assay or LPS induced TNFα production mouse model, they have not correlated the structure of the compounds tested with their relative activity in said assays and they have not tested the compounds in any disease condition as claimed. If one is to interpret Tables 1-8 as being the "All compounds exemplified...", then Tables discloses only 37 compounds wherein the A portion of the claimed compounds is a substituted 4-ter-butypyrazolyl component and the B portion of the claimed compounds is a mono or di-substituted benzene ring (e.g., quinolyl or isoquinolyl). Thus, the claimed compounds of Formula I, which have been shown to encompass an inordinate amount of compounds, would be represented by only 38 compounds with only 2 distinct cores (37 compounds with the A portion a 4-tert-butylpyrazolyl component and the B portion a mono or di-substituted benzene ring (e.g., quinolyl or isoquinolyl)). Further these compounds, if taken as exemplifying the compounds in the p38 assay and LPS assay, still are not correlated with treatment of "a disease mediated by p38" as claimed. Thus, given the breadth, the disparate nature of compounds that is presently claimed, the highly unpredictable state of the art where

many specific differences or different physicochemical properties are existed among unrelated structural compounds or even structurally related compounds, the limited number of working examples, and the insufficient amount of guidance present in the specification, one of ordinary skill in the art would be burdened with undue "painstaking experimentation study" to use for treatment of " a disease mediated by p38" with the compounds of Formula I that would be enabled in this specification (The quantity of experimentation needed to be performed by one skilled in the art is yet another factor involved in the determining whether is required to make and use the instant invention. "the test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed." In re Wands, 858 F.2d 737, 8 USPQ2d 1404 (citing In re Angstadt, 537 F.2d 489, 502-04, 190 USPQ 214, 218 (CCPA 1976))).

The examiner acknowledges that the Office does not require the present of (all) working examples to be present in the disclosure of the invention (see MPEP 2164.02). However, given the highly unpredictable state of the art and furthermore, given that the applicant does not provide sufficient guidance or direction as to how to use the full scope of the presently claimed invention without undue amount of experimentation, the Office would require appropriate disclosure, in the way of scientifically sound reasoning or the way of concrete examples, as to why the data shown is a reasonably representative and objective showing such that it was commensurate in scope with and, thus, adequately enables, the use of the elected species for the full scope of the presently claimed subject matter. Absent such evidence or reasoning, applicant

has failed to obviate the rejection of the instant claims under 35 USC 112, first paragraph (for the lack of scope of enablement).

In response to Appellant's argument that the provisional double patenting rejection is not ripe for review, the examiner recognizes that appellant cannot strip the board of its jurisdiction simply by failing to argue the merits. See E.g., In re Longi, 759 F.2d 887, 892, 225 USPQ645, 648 (Fed. Cir. 1985) (double patenting rejection over claims of three copending applications affirmed on the merits); In re Mott, 539 F.2d 1291, 1296, 190 USPQ 536, 541 (CCPA 1976) (double patenting rejection under 37 CFR § 101 over claims in a copending application was held correct on the merits but reversed because rejection was made final rather than provisional); In re Wetterau, 356 F.2d 556,558, 148 USPQ 499, 501 (CCPA 1966) (affirming provisional double patenting rejection over claims in a copending application on the merits). Accordingly, in absence of any argument, the examiner maintains that claims 50 and 52-56 are rejected provisionally under the judicially created doctrine of double patenting over claims 17-24, 26 and 30-32 of copending U.S. Application No. 09/776, 935 or claims 1, 3-4 and 7-11 of copending US. Application No. 10/086417.

(11) Related Proceedings Appendix

The appellant's statement of related proceedings appendix in the brief is correct. There are no decisions rendered by a court or the Board in any proceeding identified pursuant to paragraph (c) (1) (ii) of this section.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

Brian Kwon:bk
June 03, 2004

BRIAN-YONG S. KWON
PRIMARY EXAMINER

Conferees
Ardin Marschel, Johann Richter

ARDIN H. MARSCHEL
SUPERVISORY PATENT EXAMINER

JOHANN RICHTER
SUPERVISORY PATENT EXAMINER
GROUP 1200

Jacques Dumas et al.
400 Morgan Lane
West Haven, CT 06516